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54 Preparation of crosslinked anion exchange particles.

57 The present invention provides a process for preparing substantially water-insoluble bile acid sequesterant polymers in particulate form, preferably in spherical form, the polymer particles whenever prepared by such process, and pharmaceutical compositions comprising such polymer particles. The polymer particles, which have a bile acid sequestering efficacy greater than that of cholestyramine, preferably greater than about three times the efficacy of cholestyramine, are prepared by crosslinking one or more amine-containing polymers with one or more polyfunctional amine-reactive compounds. Also disclosed is a method for lowering blood cholesterol level in a mammal comprising oral administration of the polymer particles to the mammal.

The present invention is concerned with the preparation of crosslinked anion exchange particles, and compositions containing such particles.

It has been recognized that elevated levels of cholesterol in the blood plasma are a major risk factor of coronary heart disease in humans and that reducing plasma cholesterol level decreases the risk of coronary heart disease. Successful approaches to controlling blood cholesterol levels have included dietary modification, e.g., minimizing the intake of cholesterol-laden foods and of foods having high fat content, inhibiting cholesterol biosynthesis, and encouraging an increase in the amount of bile acids eliminated by the body.

Particulate resins, e.g., cholestyramine, described in US-A-3383281, and colestipol, described in US-A-3692895, that are capable of sequestering bile acids are known. Such resins, when orally administered to a mammalian host, form complexes with bile acid conjugates in the intestine and are effective in blocking reabsorption of bile acids from the intestine. The resin and sequestered bile acids are subsequently excreted from the body in fecal matter thereby increasing the rate at which bile acids are eliminated from the body. Other factors being equal, an increase in the rate at which bile acids are eliminated from the body tends to lower plasma cholesterol level by accelerating the conversion of cholesterol to bile acids in order to maintain a constant supply of bile acids in the body. A portion of the cholesterol for this increased synthesis of bile acids is supplied by removal of cholesterol from the blood plasma.

The bile acid sequestrants may be orally administered in various forms, typically as mixtures with food. Although the dosages of known sequestrants that are effective in lowering serum cholesterol in humans typically fall in the range of 10 to 15 grams/day, dosages of up to about 50 grams/day may be required. The particulate bile acid sequesterant resins can be unpleasant to ingest, particularly when large dosages are required and adverse side reactions (bloating, gas formation, constipation, diarrhea and the like) are common among patients to whom the resins are administered.

There has been a continuing effort in this field to minimize the unpleasant side effects associated with a therapeutically effective bile acid sequesterant regimen by developing sequestrants having increased ability to sequester bile acids and which are also effective in reducing serum cholesterol when administered at lower dosages than presently required using cholestyramine and colestipol.

While new candidate bile acid sequestrants must possess satisfactory bile acid sequestering efficacy, they must also be non-toxic to the host receiving the treatment. Some bile acid sequestrants may possess satisfactory bile acid sequestering efficacy, e.g., water-soluble polymers, however, they have been found to be cytotoxic towards the host due to sensitivity of living tissue exposed to the water-soluble bile acid sequesterant. It is, therefore, desirable to provide a bile acid sequesterant that possesses the bile acid sequestering efficacy of such water-soluble polymers but without the cytotoxic side effects which occur due to intimate contact between the sequesterant used and the living tissues exposed to the sequesterant.

One approach to providing bile acid sequestrants having the proper combination of physical properties is to polymerize functionalized monomers which are water-soluble due to their functionalized nature and to cross-link the polymer to such an extent to render it water-insoluble, thus minimizing cytotoxic effects, without hindering accessibility of the functionalized sites of the sequesterant to target bile acids to be removed.

An aim of the present invention is to provide a bile acid sequesterant with enhanced bile acid sequestering efficacy and low mammalian cytotoxicity based on a crosslinked polymer made from functionalized water-soluble monomers. A further aim of the present invention is to provide a process for preparing bile acid sequesterant polymer particles, preferably as spherical polymer particles.

According to the present invention there is provided a process for the preparation of substantially water-insoluble bile acid sequesterant polymer particles in the form of anion exchange resins, the process comprising:

- (a) polymerizing a monomer charge comprising one or more amine-containing monomers by free-radical polymerization; and
- (b) non-free-radical crosslinking with one or more polyfunctional amine-reactive compounds, the non-free radical crosslinking occurring before and/or during and/or after step (a);

to provide polymer particles that have bile acid sequestering efficacy greater than that of cholestyramine, provided that the amine-containing monomer(s) contain amine functionality that is not directly attached to a vinyl group in the case where step (b) is conducted after step (a), and further provided that step (b) occurs during step (a) in the case where the monomer charge of step (a) comprises one or more free-radical reactive polyvinyl crosslinking monomers.

The present invention also provides polymer particles prepared by the process of the invention.

The present invention further provides polymer compositions comprising polymer particles prepared by the process of the invention.

The present invention further provides pharmaceutical compositions comprising bile acid sequesterant polymer particles prepared by the process of the invention, and a pharmaceutically acceptable carrier. In this aspect the composition may further comprise a cholesterol biosynthesis-inhibiting material such as an HMG-

CoA reductase inhibitor.

In one aspect of the invention the polymerization process comprises suspension polymerization of the water-soluble amine-containing monomer(s), optionally using a sufficient amount of one or more dispersant to provide the polymer particles in spherical form.

Another aspect of the invention involves conducting the polymerization wherein crosslinking with the polyfunctional amine-reactive compound(s) occurs during formation of the polymer particles.

In another aspect of the invention the amine-containing monomer(s) is/are selected from: unsubstituted and substituted aminoalkyl (meth)acrylate esters, for example dimethylaminosthyl methacrylate; and unsubstituted and substituted aminoalkyl (meth)acrylamides, for example dimethylaminopropyl methacrylamide.

In another aspect of the present invention the polyfunctional amine-reactive compound(s) is/are selected from unsubstituted and substituted members of the following classes: dihaloalkanes, for example dihaloalkanes selected from the group consisting of 1,2-dichloroethane, 1,2-dichloropropane, 1,3-dichloropropane, 1,3-dichloro-2-propanol and 1,4-dichlorobutane; aralkyl dihalides; alkylene diesters; aryl diesters; aralkyl diesters; alkylene diacylhalides; aryl diacylhalides; aralkyl diacylhalides; dialdehydes; diepoxy-alkanes; epihalohydrins such as epichlorohydrin; and aralkyl diepoxides. Preferably, the polyfunctional amine-reactive compound(s) is/are selected from unsubstituted and substituted members of the following classes: dihalo(C<sub>1</sub>-C<sub>20</sub>)alkanes; (C<sub>6</sub>-C<sub>20</sub>)aralkyl dihalides; (C<sub>1</sub>-C<sub>20</sub>)alkylene diesters; (C<sub>6</sub>)aryl diesters; (C<sub>6</sub>-C<sub>20</sub>)aralkyl diesters; (C<sub>1</sub>-C<sub>20</sub>)alkylene diacylhalides; (C<sub>6</sub>)aryl diacylhalides; (C<sub>6</sub>-C<sub>20</sub>)aralkyl diacylhalides; (C<sub>1</sub>-C<sub>20</sub>)dialdehydes; diepoxy-(C<sub>1</sub>-C<sub>20</sub>)alkanes; epihalohydrins; and (C<sub>1</sub>-C<sub>20</sub>)aralkyl diepoxides.

The polyfunctional amine-reactive compound(s) is/are preferably used in an amount of from 0.1 to 50 mole percent, for example in an amount of from 2 to 10 mole percent, of the total monomers present.

In another aspect of the invention the polymer particles have amine functionality attached to polymer backbone through a side chain linkage group.

In yet another aspect the particles are in the form of a pharmaceutically acceptable salt.

In yet another aspect of the invention the polymer particles are in the form of a pharmaceutically acceptable salt having bile acid sequestering efficacy at least three times the efficacy of cholestyramine.

The present invention also provides a method for lowering blood cholesterol level in a mammal, which comprises oral administration to the mammal of a therapeutically effective amount, for example an amount of between about 2 milligrams and about 125 milligrams per kilo of body weight of the mammal per day, of the bile acid sequestrant polymer particles prepared according to the aforementioned process. In this embodiment, a therapeutically effective amount of a cholesterol biosynthesis-inhibiting material may also be administered to the mammal.

The anion exchange resins of the present invention may be prepared by several variations of the same process. In one variation the polymers may be produced by bulk polymerization in which the amine-containing monomer(s) is/are first mixed with one or more monomer-soluble polyfunctional amine-reactive compound, the mixture is then heated, for example on a heated plate, roll or sheet, to polymerize the mixture to a solid mass, after which the solid polymer is granulated into particles by grinding, flaking or other similar means.

In another variation of the process the polymers may be produced wherein polymerizing a monomer charge, comprising one or more amine-containing monomers, by free radical polymerization is completed to produce an uncrosslinked polymer, followed by non-free-radical crosslinking with one or more polyfunctional amine-reactive compounds to form the crosslinked polymer particles. Preferably, this type of polymer is prepared in aqueous solution and the resultant polymer may be further granulated to the desired particle size by grinding and similar procedures.

In yet another variation the polymers may be produced by suspension polymerization, preferably in aqueous media. A monomer charge comprising one or more water-soluble, amine-containing monomers, one or more monomer-soluble polyfunctional compound having functional groups capable of reacting with amine functional groups of the amine-containing monomer(s), and, optionally, one or more additional, copolymerizable monomers, is suspended in an aqueous medium and the suspension is polymerized in the presence of monomer-soluble, free-radical initiator to form polymer particles which have amine functionality. Preferably, suspension aids are used to provide polymer particles in spherical form; for example, the aqueous phase may contain dissolved inorganic salts and suitable dispersants.

In a preferred embodiment of the invention the process comprises suspension polymerizing a monomer charge comprising one or more water-soluble amine-containing monomers by free radical polymerization using one or more dispersant to provide the polymer particles in spherical form, and non-free-radical crosslinking with one or more polyfunctional amine-reactive compounds during formation of the particles to provide polymer particles that (1) have bile acid sequestering efficacy greater than that of cholestyramine and (2) that have amine functionality attached to polymer backbone through a side chain linkage group. A more preferred embodiment of the polymer particles is in the form of a pharmaceutically acceptable salt having bile acid seque-

tering efficacy at least three times the efficacy of cholestyramine.

As used herein, the terms "(meth)acrylate" and "(meth)acrylamide" refer to either the corresponding acrylate or methacrylate, and acrylamide or methacrylamide, respectively. Also, as used herein, the term "substituted" is used in conjunction with various amine-containing monomers and polyfunctional amine-reactive compounds to indicate that one or more hydrogens of these compounds has been replaced, for example, with (C<sub>1</sub>-C<sub>8</sub>)alkyl, halogen (e.g., chloro-, bromo-), hydroxyl groups and the like, except where such groups may be incompatible with functional groups already present.

Among those amine-containing monomers suitable for use in the present invention are those vinyl monomers containing amine functionality that is not directly attached to the vinyl group. Such monomers include, for example: amide monomers such as dialkylaminoalkyl acrylamides or methacrylamides (for example, dimethylaminopropyl methacrylamide), N,N-bis-(dimethylaminoalkyl) acrylamides or methacrylamides, N-β-aminoethyl acrylamide or methacrylamide, N-(methylaminoethyl)acrylamide or methacrylamide, aminoalkylpyrazine acrylamides or methacrylamides; acrylic ester monomers such as dialkylaminoalkyl acrylates or methacrylates (for example, dimethylaminoethyl acrylate or methacrylate), β-aminoethyl acrylate or methacrylate, N-(n-butyl)-4-aminobutyl acrylate or methacrylate, methacryloxyethoxyethylamine, and acryloxypropoxypropoxypropylamine; vinyl monomers such as vinyl pyridines; aminoalkyl vinyl ethers or sulfides such as β-aminoethyl vinyl ether, β-aminoethyl vinyl sulfide, N-methyl-β-aminoethyl vinyl ether or sulfide, N-ethyl-β-aminoethyl vinyl ether or sulfide, N-butyl-β-aminoethyl vinyl ether or sulfide, and N-methyl-3-aminopropyl vinyl ether or sulfide; N-acryloxyalkyl-oxazolidines and N-acryloxyalkyltetrahydro-1,3-oxazines such as oxazolidinylethyl methacrylate, oxazolidinylethyl acrylate, 3-(γ-methacryloxypropyl)tetrahydro-1,3-oxazine, 3-(β-methacryloxyethyl)-2,2-pentamethylene-oxazolidine, 3-(β-methacryloxyethyl)-2-methyl-2-propyloxazolidine, N-2-(2-acryloxyethoxy)ethyl-oxazolidine, N-2-(2-methacryloxyethoxy)-ethyl-5-methyl-oxazolidine, 3-[2-(2-methacryloxyethoxy)ethyl]-2,2-dimethyloxazolidine, N-2-(2-acryloxyethoxy)ethyl-5-methyl-oxazolidine, 3-[2-(methacryloxyethoxy)ethyl]-2-phenyl-oxazolidine, N-2-(2-methacryloxyethoxy)ethyl-oxazolidine, and 3-[2-(2-methacryloxyethoxy)ethyl]-2,2-pentamethylene-oxazolidine.

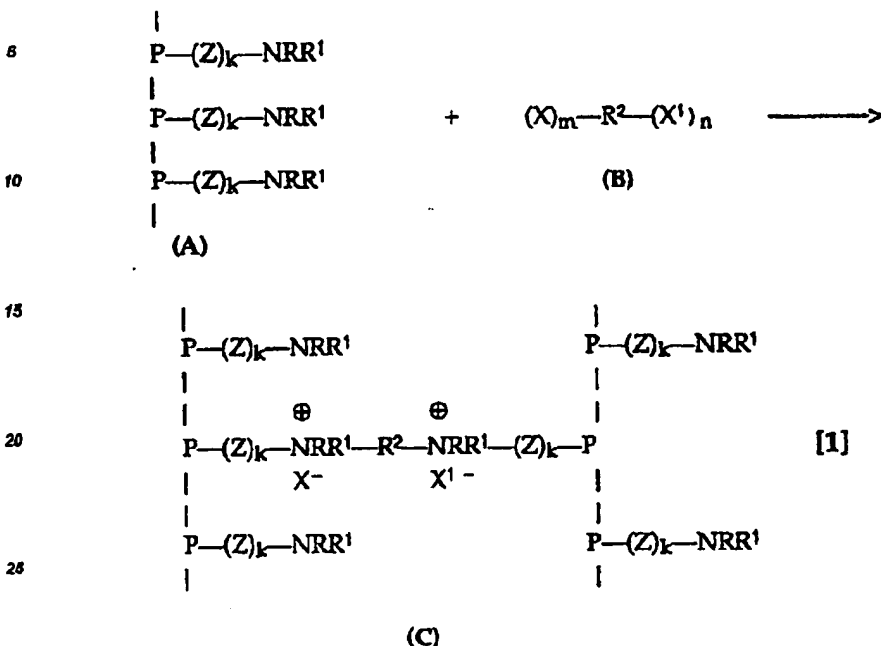
Preferred water-soluble, amine-containing monomers useful in the present invention are unsubstituted and substituted aminoalkyl (meth)acrylate esters, and unsubstituted and substituted aminoalkyl (meth)acrylamides. Included among these monomers are: dimethylaminoalkyl acrylamides and methacrylamides, N,N-bis-(dimethylaminoalkyl) acrylamides and methacrylamides, dimethylaminoalkyl acrylates and methacrylates, or mixtures including any two or more of these monomers. Most preferred are the dimethylaminoalkyl acrylamides and methacrylamides, dimethylaminoalkyl acrylates and methacrylates, and mixtures of two or more thereof, in which the alkyl group has from 2 to about 8 carbon atoms, and particularly preferred are dimethylaminopropyl methacrylamide, dimethylaminoethyl methacrylate and mixtures of two or more thereof. The water-soluble monomer(s) is/are typically present in the monomer charge as the major component; that is, the water-soluble monomer or monomers is/are typically present at a level of at least 50 weight percent by weight of the total monomers. As used herein, the term "water-soluble", as applied to monomers, indicates that the monomer has a solubility of at least about 1 gram per 100 grams of water, preferably at least about 10 grams per 100 grams of water, and more preferably at least about 50 grams per 100 grams of water.

One or more other, non-amine-containing monomers may, optionally, be present as minor components of the monomer charge; that is, such monomer(s) may be present in a total combined amount of less than about 50% by weight of the total monomers. Such non-amine-containing monomer(s) is/are preferably present at less than about 25% by weight of the total monomers. Non-amine-containing monomers useful in the present invention include those which are copolymerizable with the amine-containing monomer(s). Examples of such other monomers include, but are not limited to, aromatic monomers such as styrene and α-methylstyrene, and aliphatic monomers such as methyl acrylate, methyl methacrylate, ethyl acrylate, ethyl methacrylate, butyl acrylate, butyl methacrylate, maleic anhydride, vinyl acetate and the like, and mixtures of two or more thereof.

In addition to the presence of non-amine-containing monomers, one or more inert solvent may also be present in the monomer charge. Such inert solvent(s) may, for example, be present at less than about 80%, preferably less than about 50%, by weight of the total monomer charge. Such inert solvents are preferably present at less than about 25% by weight of the total monomer charge. Preferred inert solvents useful in the present invention include those which are themselves water-insoluble, but which are miscible with the amine-containing monomer(s). The inert solvents that combine the properties of water-insolubility and monomer-solubility are especially useful for enhancing the integrity of the spherical beads formed during the suspension polymerization of water-soluble amine-containing monomer(s). Examples of such solvents include, but are not limited to, hexane, heptane, isooctane, toluene, xylene, ethylbenzene and mixtures of two or more thereof.

In one embodiment of the present invention, crosslinker(s) of the general formula B react with amine functionality, NRR', of the amine-containing polymer (represented in part by structure A) or the corresponding amine-containing monomer(s) to produce crosslinked polymer (represented in part by structure C) according

to Equation 1:



where

$\begin{array}{c} | \\ \text{P} = \text{polymer backbone;} \\ | \end{array}$

Z = side chain linkage group;

k, m, n = zero or an integer from 1 to 3, and may be the same or different;

R, R' = (C<sub>1</sub>-C<sub>8</sub>)alkyl groups or hydrogen; or R and R' together with the nitrogen atom to which they are attached may be joined to form a saturated ring, optionally containing one or more further hetero-atoms, for example oxygen or nitrogen;

R<sup>2</sup> = (C<sub>1</sub>-C<sub>20</sub>)alkylene, aryl, (C<sub>6</sub>-C<sub>20</sub>)aryl-bis-alkylene;

X, X' = halogen, tosylate, mesylate, brosylate, nosylate, triflate, nonaflate, tresylate, epoxide (X or X' is attached to R<sup>2</sup> in C as -O-), and may be the same or different.

The side chain linkage group, Z, is any chemically stable linkage between -NRR<sup>1</sup> the polymer backbone, i.e., -NRR<sup>1</sup> is not attached directly to polymer backbone. By "chemically stable" is meant that Z does not substantially decompose or degrade during the polymerization or crosslinking reactions. When k is zero the amine functionality is attached directly to the polymer backbone. Types of side chain linkage groups suitable for use in the present invention include, for example:

an oxyalkylene group: -O-(CHR)<sub>x</sub>-,

a thioalkylene group: -S-(CHR)<sub>x</sub>-,

an alkylaminoalkyl group: -(CHR)<sub>x</sub>-NR-(CHR)<sub>x</sub>-,

an alkylene group: -(CHR)<sub>x</sub>-,

an arylalkylene group: -C<sub>6</sub>H<sub>4</sub>-(CHR)<sub>x</sub>-,

an alkoxyalkyl group: -(CHR)<sub>x</sub>-O-(CHR)<sub>x</sub>-,

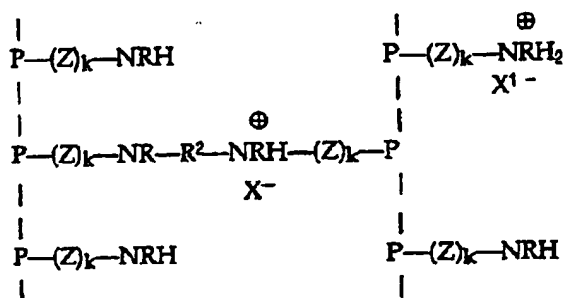
an alkylthioalkyl group: -(CHR)<sub>x</sub>-S-(CHR)<sub>x</sub>- (and corresponding sulfone and sulfoxide derivatives),

an amidoalkyl group: -C(=O)NR-(CHR)<sub>x</sub>-,

a carboxyalkyl group: -C(=O)O-(CHR)<sub>x</sub>-,

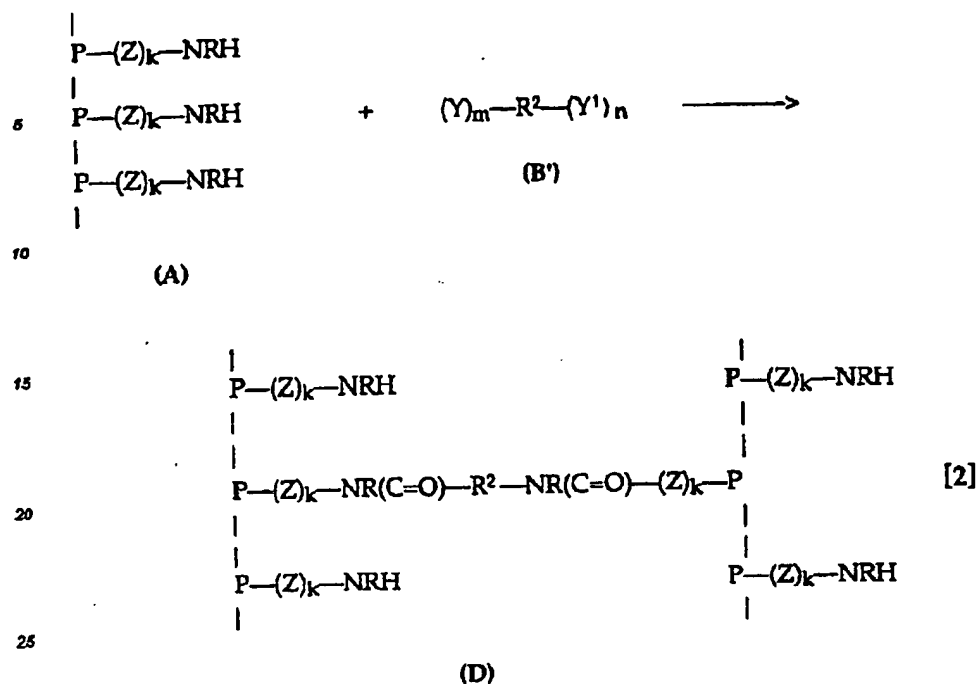
where R is as defined above and x is an integer from 1 to 10. When  $n = m = 1$ , the polyfunctional amine-reactive compound is represented by a difunctional crosslinker. Sulfur and nitrogen atoms present in the side chain linkage may participate in the crosslinking reaction with polyfunctional amine-reactive compound(s) depending on the reactivities of the particular materials involved.

When neither R nor R' in Equation 1 is hydrogen, then the crosslinking sites in the resultant polymer are represented by the quaternary ammonium salt form as illustrated in structure C. When R or R' is hydrogen, the crosslinking sites in the resultant polymer (represented in part by structure C') may be partially or totally in the free base form in the presence of excess amine functionality.



(C')

When the polyfunctional amine-reactive compound is a diester (B', where Y, Y' = carbalkoxy, represented by  $-\text{COOR}^3$ ) or diacid chloride (B', where Y, Y' = haloacyl, represented by  $-\text{COY}^2$ ), at least one R or R' of A = hydrogen,  $\text{R}^3 = (\text{C}_1-\text{C}_8)$ alkyl, and  $\text{Y}^2 = \text{halogen}$ , then the crosslinking reaction takes place according to Equation 2. When B' is a diacid chloride some portion of the amine functionality in the resultant crosslinked polymer (represented in part by structure D) will be in the  $\text{HY}^2$  salt form and when B' is a diester the amine functionality will be in the free base form with  $\text{R}^3\text{OH}$  as a byproduct of the crosslinking reaction.



When at least some of the amine functionality in A is represented by both R and R' being hydrogen, then dialdehydes may be used to crosslink the polymer. In this case, the resultant crosslinked polymer contains imine groups, known as Schiff bases when the dialdehyde is an aromatic dialdehyde, such as isophthalaldehyde, phthalaldehyde or terephthalaldehyde. Glutaraldehyde is an example of a suitable aliphatic dialdehyde.

When R or R' is hydrogen, or both R and R' are hydrogen, a Michael-type reaction (also known as conjugate addition) may be used to crosslink the polymer in the absence of free-radical polymerization conditions. Examples of crosslinkers suitable for crosslinking the polymer in this manner are ethyleneglycol diacrylate, ethyleneglycol dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane trimethacrylate and the like.

Crosslinkers useful in practicing the present invention are those compounds containing more than one amine-reactive site, i.e., any polyfunctional amine-reactive compound. Compounds suitable for use as crosslinkers in the present invention (e.g. designation B or B' in Equations 1 and 2) include unsubstituted and substituted members of the following classes: dihaloalkanes, aralkyl dihalides (such as bis(chloromethyl)benzene), alkylene diesters, aryl diesters, aralkyl diesters, alkylene diacylhalides (such as succinyl chloride), aryl diacylhalides, aralkyl diacylhalides, dialdehydes, diepoxyalkanes and aralkyl diepoxides. Polyfunctional amine-reactive compounds having mixed functional groups (e.g. where X and X' or Y and Y' are different), for example, epichlorohydrins such as epichlorohydrin or epibromohydrin, are also suitable as crosslinkers. In addition, the tosylate (*p*-toluenesulfonate), mesylate (methanesulfonate), brosylate (*p*-bromobenzenesulfonate), nosylate (*p*-nitrobenzenesulfonate), triflate (trifluoromethanesulfonate), nonaflate (nonafluorobutanesulfonate), and tresylate (trifluoroethanesulfonate) derivatives of unsubstituted and substituted difunctional alkanes and aralkanes are suitable as crosslinkers in the present invention.

Preferred dihaloalkanes are dichloroalkanes and are represented, for example, by those selected from the group consisting of 1,2-dichloroethane, 1,2-dichloropropane, 1,3-dichloropropane, 1,3-dichloro-2-propanol and 1,4-dichlorobutane. Preferred alkylene diesters are dimethyl malonate, dimethyl succinate, diethyl glutarate, diethyl adipate, diethyl suberate, diethyl azelate and diethyl sebacate.

The amount of crosslinking provided by the polyfunctional amine-reactive compound(s) used in the polymers of the present invention may be any amount that is effective to render the polymer substantially insoluble in water, e.g., from about 0.1 to about 50 mole percent, preferably from about 0.5 to about 20 mole percent, of total monomers, while maintaining efficacy as a bile acid sequestrant. When the term "total monomers" is used, reference is being made to the amine-containing monomer(s), the polyfunctional amine-reactive compound(s) used as crosslinkers, and any other optional vinyl- or polyvinyl-containing monomer(s). Most prefer-



ably, the amount of crosslinking approaches the minimum amount effective to render the polymer substantially insoluble in water, e.g., from about 2 mole percent to about 10 mole percent of total monomers present, while maintaining high efficacy as a bile acid sequestrant.

In addition to the polyfunctional amine-reactive crosslinker compound(s), the polymers of the present invention may also be crosslinked with minor amounts of one or more conventional free-radical reactive polyvinyl monomers, i.e., less than about 10 mole percent, preferably less than about 2 mole percent, and most preferably less than about 0.5 mole percent, based on total monomers. Conventional polyvinyl monomers, which copolymerize under free-radical conditions, include, for example, divinylbenzene, trivinylbenzene, divinyltoluene, divinylpyridine, ethyleneglycol diacrylate, ethyleneglycol dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane trimethacrylate, diethyleneglycol divinyl ether and the like.

While not wishing to be bound by theory, we believe that, in the case of the present invention, there is little or no heterogeneity incorporated into the polymer backbone since the crosslinker(s) does not act as a free-radical reactive comonomer during the polymerization of the amine-containing monomer(s). Instead, the crosslinking reaction takes place at sites away from the polymer backbone by nucleophilic displacement reaction mechanisms. The process of the present invention provides a greater chance for random homogeneous distribution of the crosslinking sites in the resultant crosslinked amine-containing polymer particles when compared to conventional crosslinked particles prepared by free-radical copolymerization (such as cholestyramine and others prepared with polyvinyl comonomers) or by crosslinking directly through polymer backbone sites (such as colestipol). In addition to the more homogeneous distribution of crosslink sites, it is believed that the process of the present invention allows for (1) greater control over molecular dimensions of the crosslinking moiety and, subsequently, the molecular flexibility of the resultant crosslinked structure when compared to conventional crosslinked polymers, resulting in (2) bile acid sequestering efficacy greater than that of cholestyramine, preferably at least three times, and most preferably, at least four times the efficacy of cholestyramine.

The mechanism by which polymers of the present invention are crosslinked involves reaction between the nucleophilic amine groups of the polymer side chains with amine-reactive sites of the crosslinker molecule; these reactions may involve quaternization of the side chain amine groups or, in the case of primary or secondary amine groups, acylation, alkylation, condensation or conjugate addition reactions. The timing of the actual crosslinking reaction relative to the formation of polymer may vary depending upon the reactivity of the polyfunctional amine-reactive compound(s) and the amine-containing monomer(s). Crosslinking may occur before, during or after the actual polymerization of the amine-containing monomer(s) or any combination thereof. In the case of aqueous phase suspension polymerization, it is preferred that at least some of the crosslinking occurs during the polymerization of amine-containing monomer(s) to facilitate the formation of water-insoluble spherical particles. Polymers of the present invention in the form of spherical particles are preferred because of the ease of handling during isolation, cleaning and washing of the polymer; however, other forms of the polymers, e.g., precipitation, powdered, etc., are equally efficacious regarding bile acid sequestering capacity.

Polymerization initiators in the present invention include monomer-soluble initiators such as peroxides, hydroperoxides and related initiators, as for example benzoyl peroxide, *tert*-butyl hydroperoxide, cumene peroxide, tetralin peroxide, acetyl peroxide, caproyl peroxide, *tert*-butyl peroctoate, *tert*-butyl perbenzoate, *tert*-butyl diphenylphthalate, methyl ethyl ketone peroxide and the like. Also useful are azo initiators such as azodisobutyronitrile, azodisobutyramide, 2,2'-azo-bis(2,4-dimethylvaleronitrile), azo-bis( $\alpha$ -methylbutyronitrile) and dimethyl-, diethyl- or dibutyl azo-bis(methylvalerate). Preferred initiators are the azo initiators, and particularly preferred is 2,2'-azo-bis(2,4-dimethylvaleronitrile). Preferred use levels of peroxide and azo initiators are from about 0.01% to 3% by weight, and from about 0.01% to about 2% by weight, respectively, based on the total weight of vinyl monomers.

Salts useful for reducing solubility of the amine-containing monomer(s) in aqueous phase polymerizations include water-soluble, non-reactive inorganic salts of a monovalent, divalent or aluminum cation and a monovalent or divalent anion, for example sodium, potassium, lithium and ammonium salts of chloride, bromide, iodide, sulfate, carbonate and nitrate and the magnesium and calcium salts of chloride, bromide, iodide and nitrate. Preferred salts are sodium chloride, sodium sulfate and sodium nitrate. The salt is preferably dissolved in the aqueous medium at levels from about 5% by weight, based upon the total aqueous phase weight, to saturation of the salt in the aqueous phase. The term "non-reactive," as applied to the salts herein, means that the salt does not react chemically with water, the monomers or the polymers formed from the monomers.

The preferred dispersants useful for making the anion exchange resin particles of the present invention are nonionic surfactants having a hydroxyalkylcellulose backbone, a hydrophobic alkyl side chain containing from 1 to about 24 carbon atoms, and an average of from about 1 to about 8, preferably from about 1 to about 5, ethylene oxide groups substituting each repeating unit of the hydroxyalkylcellulose backbone, the alkyl side chains being present at a level of from about 0.1 to about 10 alkyl groups per 100 repeating units in the hydroxyalkylcellulose backbone. The alkyl group in the hydroxyalkylcellulose may contain from 1 to about 24 car-

bons, and may be linear, branched or cyclic. More preferred is a hydroxyethylcellulose containing from about 0.1 to about 10 (C<sub>18</sub>)alkyl side chains per 100 anhydroglucose units and from about 2.5 to about 4 ethylene oxide groups substituting each anhydroglucose unit. A particular advantage of these dispersants is that the spherical polymer particles of the present invention produced using them are not agglomerated, i.e., clumps of particles do not adhere to one another; agglomeration occurs when unprotected or poorly protected particles collide during the polymerization process.

Typical use levels of dispersants are from about 0.01 to about 4% by weight, based upon the total aqueous-phase weight.

Other dispersants useful for making the anion exchange resin particles of the present invention include finely divided particles such as silica, clays, ground ion exchange resins or ground, crosslinked, suspension copolymers without ion exchange functionality, and inorganic salts such as calcium hydroxyphosphate, particularly in combination with hydroxyapatite. The inorganic salts may or may not be fully soluble in water, and where they are not fully soluble they may behave similarly to the finely divided particles. Still other dispersants useful for making the anion exchange resin particles of the present invention are polymers containing hydrophilic backbones, which can orient their lipophilic portions to the monomer phase and their hydrophilic portions to the aqueous phase at the interface of the two phases. These polymeric dispersants include celluloses, polyvinyl pyrrolidones, polyvinyl alcohols, starches and the like. Mixtures of dispersants may also be used. These other dispersants tend to be less preferred, as they tend to produce a somewhat greater amount of agglomerated or otherwise undesirable material.

Bile acid sequestrant polymers of the present invention may be prepared in macroporous or macroreticular form according to known methods by conducting the polymerization in the presence of precipitants, such as those disclosed in Maltzner *et al.*, US-A-4256840. The precipitant may, for example, be present in ratios from about 20 parts per 100 parts of monomer, i.e., 20% on monomer, to about 600 parts per 100 parts of monomer, i.e., 600% on monomer, depending on the crosslinking level and precipitant used. Suitable precipitants for preparing macroporous or macroreticular polymers are those materials that are solvents for the monomer and non-solvents for the resultant crosslinked polymer. Preferred precipitants include: dialkyl ketones, e.g., methyl isobutyl ketone, diisobutyl ketone and the like; (C<sub>4</sub>-C<sub>10</sub>)alcohols, e.g., *t*-amyl alcohol, 2-ethylhexanol, methylisobutyl carbinol and the like; (C<sub>6</sub>-C<sub>8</sub>)alkanes, e.g., heptane, isooctane and the like; and (C<sub>7</sub>-C<sub>10</sub>)aromatic hydrocarbons, e.g., toluene, xylene and the like.

Uncrosslinked poly(dimethylaminopropylmethacrylamide), while exhibiting efficacy as a bile acid sequestrant (relative to cholestyramine), has shown evidence of toxicity when orally administered to rats, monkeys and dogs. The crosslinked bile acid sequestrants of the present invention exhibit reduced toxicity toward mammalian tissue relative to linear, i.e., uncrosslinked poly(dimethylaminopropylmethacrylamide).

Preferably, the bile acid sequestrants of the present invention exhibit anion exchange capacities of greater than about 3 milliequivalents per gram of dry polymer (meq/g) and, more preferably, greater than about 4 meq/g. Most preferably, the bile acid sequestrants of the present invention exhibit anion exchange capacities of about 5 meq/g to about 6 meq/g.

Bile acid sequestrants of the present invention may be used in the form of free bases or in the form of pharmaceutically acceptable acid salts, or mixtures thereof. Pharmaceutically acceptable acid salts are those whose anions, when used in therapeutically effective amounts, are nontoxic to the organism to whom the salts are administered. Examples of such salts are those derived from mineral acids such as hydrochloric and phosphoric, or organic acids such as acetic, citric, lactic and malonic. The various salt forms of the present invention may be prepared by dissolving the acid in a suitable solvent, e.g., water or a solution of water and an alcohol, treating the free base with the solution to form the salt and then isolating the insoluble salt from the solution.

Hydrated, i.e., water-swollen, particles exhibiting a mean particle diameter from about 10 microns to about 400 microns, preferably from about 10 to about 200 microns, are a preferred form of the polymers prepared by the process of the present invention for use as bile acid sequestrants.

In general, bile acid sequestrants of the present invention are used for lowering blood cholesterol level in a mammal by oral administration of a therapeutically effective amount of the bile acid sequestrant to the mammal. The dosage of the sequestrants that will be most suitable for reduction of blood cholesterol level will vary with the form of administration, the particular embodiment of sequestrant, and the physiological characteristics of the host to which the sequestrant is administered. In general the amount administered is between about 2 and about 125 milligrams per kilogram (mg/kg) of body weight of the mammal per day. Based on physiological studies with beagle dogs (as described in Example 5), it is expected that the therapeutic dosage in humans will generally be from about 2 to about 125 mg/kg of body weight per day. This would correspond to a dosage for an 80 kg human host of about 0.2 to about 10 grams/day. It is expected that more widely used dosages will be from about 35 to about 60 mg/kg of body weight per day corresponding to about 2.5 to about 4 grams/day for an 80 kg host.

Pharmaceutical compositions of the present invention may be prepared by combining (1) the bile acid sequestrant polymer particles with (2) a pharmaceutically acceptable carrier. Bile acid sequestrants of the present invention can be orally administered in any suitable way, including in neat form or in the form of pharmaceutical compositions in which the sequestrant is combined with pharmaceutically acceptable carriers, for example, in the form of tablets, capsules, particles, i.e., granules or powders, or as aqueous suspensions. In the case of tablets for oral use, commonly used carriers such as lactose and corn starch, and lubricating agents such as magnesium stearate, may be added. For oral administration in capsule form useful diluents include, e.g., lactose and dried starch. When aqueous suspensions are required for oral use the active ingredient is combined with emulsifying and suspending agents. If desired, sweetening and flavoring agents may be added. Particulate forms of the sequestrant may be administered as a mixture with food items such as applesauce, stewed fruits, juices and cereals.

Bile acid sequestrants of the present invention can be used in conjunction with other treatments that are designed to lower the level of cholesterol in the blood. Preferred pharmaceutical compositions comprise a sequestrant of the present invention used in combination with a material that inhibits cholesterol biosynthesis. Examples of such materials would include but are not limited to HMG-coenzyme A (HMG-CoA) reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthase inhibitors. More preferred pharmaceutical compositions comprise a HMG-CoA reductase inhibitor as the cholesterol biosynthesis-inhibiting material. Illustrative of such HMG-CoA reductase inhibitors are lovastatin, simvastatin, pravastatin and fluvastatin. Examples of HMG-CoA synthase inhibitors are  $\beta$ -lactone derivatives,  $\beta$ -lactam derivatives and substituted oxacyclopentane analogues. Other cholesterol level-lowering agents that may be administered in conjunction with the sequestrants of the present invention include niacin, probucol, the fibric acids (clofibrate and gemfibrozil) and LDL-receptor gene inducers.

The following Examples are presented to illustrate certain embodiments of the invention. All ratios and percentages given herein are by weight unless otherwise specified, and all reagents used in the Examples are of good commercial quality unless otherwise specified.

#### EXAMPLE 1

This Example illustrates the preparation of spherical crosslinked particles of the present invention from water-soluble dimethylaminopropyl methacrylamide (DMAPMAM) monomer that has been crosslinked with the difunctional amine-reactive compound 1,3-dichloropropane.

The dispersant used was a modified hydroxyethylcellulose which was characterized by substitution with about 4.0 moles of ethylene oxide per anhydroglucose unit and approximately 0.7 - 1.0 cetyl groups per 100 anhydroglucose units, a molecular weight of approximately 300,000 and a viscosity in 1% aqueous solution of approximately 400 megaPascals.

An aqueous solution was prepared by weighing 99.4 g sodium chloride, grinding approximately 6 g of this sodium chloride in a mortar with 1.5 g dispersant to a homogeneous mixture. The unground sodium chloride was added, with stirring, to 274.1 g deionized water at about 55°C. The ground sodium chloride-dispersant mixture was added slowly to the water, which was then stirred at 55°C until all the solids had dissolved.

A monomer mixture was made by mixing 67.0 g DMAPMAM, 3.44 g 1,3-dichloropropane, 56.2 g o-xylene and 0.687 g 2,2'-azo-bis-(2,4-dimethylvaleronitrile). The difunctional amine-reactive compound content, based on the total monomer weight, was 5% (7.3 mole %).

The aqueous phase was placed in a 1-liter round-bottomed flask equipped with 2-blade agitator and stirred at 55°C. The monomer mixture was transferred to the reactor vessel and stirred while maintaining a temperature of 55°C for 14 hours, after which the solids were drained free of liquid and washed three times with water to remove the salt and most of the xylene.

The washed resin was then dried under vacuum at 60°C and ground to a particle size of less than about 200 $\mu$ . The recovery of dried resin was about 80-85%. Electron Spectroscopy for Chemical Analysis (ESCA) indicated the presence of charged (quaternary) nitrogen and neutral (amide + amine) nitrogen.

#### EXAMPLE 2

This Example illustrates the preparation of spherical crosslinked particles of the present invention from DMAPMAM monomer that has been crosslinked with the difunctional amine-reactive compound 1,3-dichloro-2-propanol.

The spherical copolymer beads of this Example were prepared using the same procedure as that of Example 1, except that 121.8 g of DMAPMAM, 6.25 g of 1,3-dichloro-2-propanol, 1.25 g of 2,2'-azo-bis-(2,4-dimethylvaleronitrile) and no xylene were used. The difunctional amine-reactive compound content, based on

the total monomer weight, was 5% (6.5 mole %). The recovery of dried resin was 116 g (93%). ESCA indicated the presence of charged (quaternary) nitrogen and neutral (amide + amine) nitrogen.

#### EXAMPLE 3 (comparative)

In a manner similar to that of Example 1, a sample of crosslinked poly(dimethylaminopropylmethacrylamide) in the form of porous, spherical beads was prepared by copolymerizing DMAPMAM with a conventional polyvinyl crosslinker, divinylbenzene (DVB).

A monomer mixture was made by mixing DMAPMAM and DVB (55% active (by weight), 45% ethylvinylbenzene); no *o*-xylene was used. A mixed initiator solution (30% by weight in acetone) based on 2,2'-azo-bis-(2,4-dimethylvaleronitrile) and 2,2'-azo-bis-(2-methylbutanenitrile) was prepared; the 2,2'-azo-bis-(2,4-dimethylvaleronitrile) initiator was used at 0.7% by weight on monomers and the 2,2'-azo-bis-(2-methylbutanenitrile) initiator was used at 0.3% by weight on monomers.

The aqueous phase containing dispersant (sodium sulfate was used in place of sodium chloride as described in Example 1) was placed in a round-bottomed flask equipped with agitator. The monomer mixture was transferred to the reactor vessel and heated to 72°C with stirring. The initiator solution was then added and the temperature was maintained at 72°C for 2.5 hours. The temperature was raised to 80°C and held for an additional 3 hours and then raised to 100°C and held for another 3 hours. The solids were drained free of liquid and washed thoroughly to remove salt after cooling the reaction mixture. The washed resin was then dried at 60°C in a convection oven and ground to a particle size of less than about 200 $\mu$ .

In this fashion, 3 different polymers were prepared crosslinked with different levels of DVB. Sample 3A contained 1 mole percent DVB, sample 3B contained 3 mole percent DVB and sample 3C contained 5 mole percent DVB.

#### EXAMPLE 4 (comparative)

In a manner similar to that of Example 1, a sample of crosslinked poly(dimethylaminopropylmethacrylamide) in the form of macroporous, spherical beads was prepared by copolymerizing DMAPMAM with conventional polyvinyl crosslinkers, divinylbenzene (DVB) and diethyleneglycol divinyl ether (DEGDVE).

A monomer mixture was made by mixing DMAPMAM, DVB (80% active (by weight), 20% ethylvinylbenzene), DEGDVE, 2,2'-azo-bis-(2,4-dimethylvaleronitrile) initiator (1% by weight of total monomer) and *o*-xylene (91% by weight on monomers). The crosslinker concentration was 4% DVB and 0.5% DEGDVE by weight of total monomer (5.7 mole percent total divinyl crosslinker).

The polymerization and polymer workup was conducted as described in Example 1, except that residual *o*-xylene was removed by steam sweep distillation.

#### EXAMPLE 5

The efficacy of the crosslinked copolymer of the present invention as a bile acid sequestrant was evaluated in beagle dogs. Beagle dogs weighing 9 to 11 kg each were fed a semi-synthetic, low cholesterol diet once per day in a quantity (200 to 300 grams/dog/day) that stabilized the body weight of the respective dogs. The semi-synthetic diet included 32.01% vitamin free casein; 43.14% dextrose; 12.42% lard; 2.39% cod liver oil; 2.72% calcium phosphate; 4.92% cella flour; and 2.39% hegested vitamin mix No. 14.

Baseline plasma cholesterol levels were assessed for each dog by feeding the semi-synthetic diet without a bile acid sequestrant for six months and measuring plasma cholesterol levels on blood samples taken twice per week. After the baseline serum cholesterol levels were established, cholestyramine bile acid sequestrant was mixed with the diet (at dosages of 3, 6 and 12 grams/dog/day) plasma cholesterol levels were measured twice a week for four weeks to characterize the relationship between cholestyramine dosage and serum cholesterol levels for each dog.

Following derivatization of the dose/response relationship, the dogs were maintained on a regimen of 12 grams cholestyramine/dog/day until a copolymer of the present invention was substituted for the cholestyramine in the diet at a dosage of either 3 grams/dog/day or 6 grams/dog/day. The dogs were fed the copolymer of the present invention and the plasma cholesterol levels of the dogs were measured daily for four weeks. The serum cholesterol level of dog fed a bile acid sequestrant stabilizes at a level below to baseline level. The relative efficacy of the crosslinked bile acid sequestrant of the present invention and of a control dosage of 12 grams cholestyramine/day was quantified by calculating an efficacy factor ("EF") according to Equation 3:

$$EF = ((N - B)/(N - A))(12/X) \quad [3]$$

wherein:

EF = efficacy factor

N = serum cholesterol level in milligrams cholesterol/deciliter serum (mg/dl) on the semi-synthetic diet without a bile acid sequestrant;

A = serum cholesterol level (mg/dl) on semi-synthetic diet including 12 grams cholestyramine/day;

5 X = (grams dosage of bile acid sequestrant of the present invention as bile acid sequestrant/day) included in serum synthetic diet; and

B = serum cholesterol level (mg/dl) on semi-synthetic diet including X grams of crosslinked bile acid sequestrant of the present invention.

The sequestrant of Example 2 and Comparative Examples 3A, 3B, 3C and 4 were each tested in beagle dogs according to the above method. A sample of uncrosslinked poly(dimethylaminopropylmethacrylamide) prepared by aqueous phase solution polymerization and having a number average molecular weight of 281,000 and a weight average molecular weight of 588,000 was also tested according to this procedure and is listed as sample 5A in the table below. Results are set forth below in Table 1 as the EF, calculated according to Equation 3 for each of the sequestrants tested, along with the dosage administered, expressed as grams sequestrant per dog per day (g/dog/day) and a number (Dog No.) identifying the dog to which the dosage was administered.

The results in Table 1 show that the bile acid sequestrant of the present invention (Example 2) possesses enhanced efficacy over that of sequestrants made with polyvinyl crosslinker (Examples 3A, 3B, 3C and 4) or with no crosslinker (Example 5A).

TABLE 1

Mole Percent Divinyl Crosslinker	Mole Percent Non-Vinyl Crosslinker	Example No.	Dog No.	Dosage (g/dog/day)	EF
0	6.5	2	205	3	4
1.0	0	3A (comparative)	209	3	1.3
3.0	0	3B (comparative)	206	3	1.7
5.0	0	3C (comparative)	205	3	2.1
5.7	0	4 (comparative)	301	3	2.7
0	0	5A (uncrosslinked)	208	8	3.2

#### EXAMPLE 6

A suspension of particles of the sequestrant in deionized water was prepared. The suspension was serially diluted into serumless culture medium. The most concentrated suspension tested was 1000 micrograms sequestrant per milliliter suspension ( $\mu\text{g/ml}$ ).

Exponentially growing Chinese hamster ovary (CHO) cell cultures were treated with the sequestrant dilutions for three hours. The cultures were gently rocked on a rocker platform during treatment in an attempt to maintain a uniform suspension over the cells for the entire treatment period. Negative controls, i.e., CHO cell cultures treated with serumless culture medium, and solvent controls, i.e., CHO cell cultures treated with 1% deionized water in serumless culture medium, were included.

Treatment was terminated by washing the cultures twice with Dulbecco's phosphate buffered saline and cells were allowed to recover in McCoy's 5A medium containing 10% fetal bovine serum for 0, 5 or 21 hours, i.e., 3, 8 or 24 hours from the beginning of treatment.

Cells were harvested at 3 and 24 hours by treating with trypsin-EDTA and scraping the cell monolayers from the culture flasks. The harvested cells were counted by Coulter counter to determine relative reductions in cell numbers. At selected doses, Trypan blue exclusion counts were conducted using a hemacytometer to determine cell viability to control for the possibility that some dead cells may have been counted with the Coulter counter. No cell counts were conducted at 8 hours, but the culture monolayers were examined for evidence of toxicity under an inverted microscope.

The sequestrants of Example 2 and comparative Example 5A (uncrosslinked) were each tested for cytotoxicity using the procedure set forth above. The results of cytotoxicity testing are set forth below in Table 2

as an  $ED_{50}$  value in  $\mu\text{g/ml}$  for each sequestrant tested, wherein the  $ED_{50}$  values indicate the minimum dosage of the respective sequestrant effective to kill 50% of the cells in the cell culture treated.

The results in Table 2 show that the bile acid sequestrant of the present invention (Example 2) possesses greatly reduced toxicity compared to that of a sequestrant made with no crosslinker (Example 5A). Materials with  $ED_{50}$  values of 100  $\mu\text{g/ml}$  or greater are generally considered non-toxic, and those with values below 100  $\mu\text{g/ml}$  are considered toxic with the degree of toxicity increasing as the value of  $ED_{50}$  decreases further below 100  $\mu\text{g/ml}$ .

TABLE 2

Example No.	$ED_{50}$ ( $\mu\text{g/ml}$ )
2	> 100
5A	10.0

### Claims

1. A process for the preparation of substantially water insoluble bile acid sequestrant polymer particles, which comprises:
  - (a) polymerizing a monomer charge comprising one or more amine-containing monomers by free-radical polymerization; and
  - (b) non-free-radical crosslinking with one or more polyfunctional amine-reactive compounds, the non-free radical crosslinking occurring before and/or during and/or after step (a);
 to provide polymer particles that have bile acid sequestering efficacy greater than that of cholestyramine, provided that the amine-containing monomer(s) contain amine functionality that is not directly attached to a vinyl group in the case where step (b) is conducted after step (a), and further provided that step (b) occurs during step (a) in the case where the monomer charge of step (a) comprises one or more free-radical reactive polyvinyl crosslinking monomers.
2. A process as claimed in claim 1, wherein the polymerization is conducted as a suspension polymerization and the amine-containing monomer(s) is/are water-soluble.
3. A process as claimed in claim 2, which further comprises the use of one or more dispersant during the polymerization in an amount sufficient to provide the polymer particles in spherical form.
4. A process as claimed in any preceding claim, wherein:
  - (i). crosslinking occurs during formation of the polymer particles; or
  - (ii). step (a) is completed to produce uncrosslinked polymer particles, followed by step (b).
5. A process as claimed in any preceding claim, wherein the polyfunctional amine-reactive compound(s) is/are used in an amount from 0.1 to 50 mole percent, for example in an amount from 2 to 10 mole percent, of total monomers present.
6. A process as claimed in any preceding claim, wherein the amine-containing monomer(s) is/are selected from: unsubstituted and substituted aminoalkyl (meth)acrylate esters, for example dimethylaminoethyl methacrylate; and unsubstituted and substituted aminoalkyl (meth)acrylamides, for example dimethylaminopropyl methacrylamide.
7. A process as claimed in any preceding claim, wherein the polyfunctional amine-reactive compound(s) is/are selected from unsubstituted and substituted members of the following classes: dihaloalkanes, for example dihaloalkanes selected from the group consisting of 1,2-dichloroethane, 1,2-dichloropropane, 1,3-dichloropropane, 1,3-dichloro-2-propanol and 1,4-dichlorobutane; aralkyl dihalides; alkylene diesters; aryl diesters; aralkyl diesters; alkylene diacylhalides; aryl diacylhalides; aralkyl diacylhalides; dialdehydes; diepoxyalkanes; epihalohydrins, for example epichlorohydrin; and aralkyl diepoxides.

8. A process as claimed in any preceding claim, wherein the polymer particles have amine functionality attached to polymer backbone through a side chain linkage group.
- 5 9. A process as claimed in any preceding claim, wherein the polymer particles are in the form of a pharmaceutically acceptable salt, for example having a bile acid sequestering efficacy at least three times the efficacy of cholestyramine.
- 10 10. A process as claimed in any preceding claim, wherein the amine-containing monomer(s) is dimethylaminopropyl methacrylamide, and the polyfunctional amine-reactive compound(s) is a substituted dihaloalkane, for example 1,3-dichloropropane or 1,3-dichloro-2-propanol.
11. A pharmaceutical composition, which comprises polymer particles prepared by a process as claimed in any preceding claim, and a pharmaceutically acceptable carrier.
- 15 12. A pharmaceutical composition as claimed in claim 11, which further comprises a cholesterol biosynthesis-inhibiting material, for example an HMG-CoA reductase inhibitor.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 95 30 0150

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 6)
A	FR-A-2 208 920 (BASF) ---		C08F20/34 A61K31/785
A	EP-A-0 459 632 (ROHM AND HAAS CO.) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 6)
			C08F
The present search report has been drawn up for all claims			
Place of search <b>THE HAGUE</b>		Date of completion of the search <b>11 May 1995</b>	Examiner <b>Cauwenberg, C</b>
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background D : non-written disclosure P : prior art document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	

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